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Applicant	Ethicon Inc.
Established Name	Fibrin Sealant Patch
Trade Name	EVARREST
Pharmacologic Class	Topical fibrin sealant
Formulation(s), including Adjuvants, etc	Human fibrinogen and human thrombin embedded in a flexible composite patch component consisting of oxidized regenerated cellulose (ORC) and polyglactin 910 (PG910).
Dosage Form(s) and Route(s) of Administration	Absorbable patch; Topical use only
Dosing Regimen	Apply topically to bleeding site with manual compression for 3 minutes. Each 2 x 4 inch (5.1 x 10.2 cm) patch contains 55.5 mg per square inch (8.6 mg per square cm) human fibrinogen and 241.9 Units per square inch (37.5 Units per square cm) human thrombin.
Indication(s) and Intended Population(s)	Use with manual compression as an adjunct to hemostasis in adult and pediatric patients undergoing surgery, when control of bleeding by conventional surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical.

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GLOSSARY

Abbreviation	Definition
AES	All Enrolled Set
AESI	Adverse event of special interest
BLA	Biologics License Application
BMI	Body mass index
CI	Confidence interval
CRO	Contract Research Organization
CSR	Clinical study report
DF	Distribution-free
FAS	Full Analysis Set
FDA	Food and Drug Administration
ITT	Intent-to-treat
MPD	Major protocol deviation
ORC	Oxidized regenerated cellulose
PG910	Polyglactin 910
PMR	Post-Marketing Requirement
PP	Per Protocol
PREA	Pediatric Research Equity Act
PSP	Pediatric Study Plan
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sBLA	Supplemental Biologics License Application
SD	Standard deviation
SOC	System organ class
STN	Submission Tracking Number
SUSAR	Suspected unexpected serious adverse reaction
TBS	Target bleeding site
TEE	Thromboembolic event
TTH	Time to hemostasis
UK	United Kingdom
US	United States

1. EXECUTIVE SUMMARY

EVARREST Fibrin Sealant Patch is a sterile, bio-absorbable combination product, made from a flexible composite Matrix, coated with Human Fibrinogen and Human Thrombin. EVARREST was originally approved on December 5, 2012, as an adjunct to hemostasis for soft tissue (open retroperitoneal, intra-abdominal, pelvic and noncardiac thoracic) bleeding, and was subsequently approved for solid organ (liver, (b) (4)) bleeding on March 26, 2015. On September 30, 2016, EVARREST received approval to further expand the clinical indication to include thoracic (b) (4) surgery and cardiovascular surgery.

This efficacy supplement Biologics License Application (sBLA) presented results from an open-label, prospective, non-controlled, multicenter clinical study in the US and the UK among pediatric subjects undergoing liver/soft-tissue surgery (study BIOS-16-001 with N=35) and a randomized, controlled study among the same population in the UK (study 400-12-004 with N=40) to fulfill the Pediatric Research Equity Act (PREA) Post-Marketing Requirement (PMR) and expand the clinical indication to adjunctive hemostasis in both the adult and pediatric population.

The primary efficacy endpoint in both studies was time to hemostasis (TTH). In study BIOS-16-001, TTH was defined as the absolute time elapsed from the identification of the target bleeding site (TBS) to the last observed moment of detectable bleeding. In study 400-12-004, TTH was defined as the absolute time elapsed from randomization to the last observed moment of detectable bleeding at the TBS. In study BIOS-16-001, the median TTH in the All Enrolled Set (AES) was 4.0 minutes (mean [SD]: 7.77 [11.150] minutes). In study 400-12-004, the median TTH was 4.0 minutes in both the EVARREST and SURGICEL groups in the AES (EVARREST mean [SD]: 9.88 [25.226] minutes; SURGICEL mean [SD]: 7.75 [8.197] minutes). The efficacy results were consistent across the two studies, supporting the robustness of the primary efficacy findings.

There was no death reported during both studies. In study BIOS-16-001, a total of 13 serious adverse events (SAEs) were reported. In study 400-12-004, 7 SAEs were reported in the EVARREST group and 8 in the SURGICEL group. Adverse events of special interest (AESIs) included thromboembolic events (TEEs) and rebleeding following application of the EVARREST patch. No TEEs were identified in either study. Rebleeding events were reported in both studies, with 3 events in study BIOS-16-001, and 1 event in the EVARREST group and 4 events in the SURGICEL group in study 400-12-004.

Hypothesis testing was neither performed nor reported on either study. Based on the efficacy data generated across studies BIOS-16-001 and 400-12-004, the consistent findings from the descriptive analyses across both studies provide sufficient evidence to support approval of Fibrin Pad as an adjunct to hemostasis in a broad range of surgical scenarios in both adult and pediatric subjects in this efficacy supplement Biologics License Application.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Managing hemostasis during surgery is critical, as bleeding can vary widely in type, severity, and location. Effective hemostatic control has shaped the development of modern surgical techniques. Choosing the right method to control bleeding depends on factors such as the source, accessibility, tissue type, and the patient's condition. While the body normally achieves hemostasis through the coagulation cascade, surgeons rely on methods like sutures, clips, or cauterization, and when these are insufficient, surgeons use adjunctive products such as absorbable hemostats or active agents like thrombin and fibrin sealants (Chiara et al., 2018; Tompeck et al., 2020).

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 1. Summary of major Pre- and Post-submission regulatory activities

Date	Milestone
12/05/2012	Original BLA 125392/0 approved
03/26/2015	New indication sBLA 125392/33 approved
09/30/2016	New indication sBLA 125392/163 approved
12/08/2025	Post marketing sBLA 125392/645 received
01/22/2026	sBLA 125392/645 Filing Meeting
05/07/2026	sBLA 125392/645 Internal Mid-cycle Meeting
10/08/2026	sBLA 125392/645 FDA Action Letter Goal Date

(Source: adapted from sBLA 125392/645; FDA reviewer's summary)

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The primary source of evidence to support the efficacy and safety of the proposed product comes from study BIOS-16-001 and study 400-12-004, which are the focus of this review memo.

Reviewer's Note: A Pediatric Study Plan (PSP) was submitted and agreed upon by FDA under BLA 125392/163. The PSP included a clinical trial to evaluate the safety and

efficacy of Fibrin Pad as an adjunct to control mild to moderate soft tissue or parenchymal bleeding during surgery in pediatric patients from 1 month to less than 18 years of age. Specifically, the approved PSP required a trial enrolling 35 pediatric subjects treated with EVARREST for surgical hemostasis, the results of which were to be integrated with those from an earlier European study (400-12-004). That European study included 20 subjects randomized to EVARREST and 20 subjects randomized to the control (SURGICEL).

However, during the review of BLA 125392/645, the clinical team determined that the efficacy results from these two studies would be evaluated separately, rather than pooled, due to differences in study design.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The basis of this statistical memo includes review of clinical study reports, datasets, protocols, and statistical analysis plans submitted under Module 2 and Module 5 of BLA 125392/645.

5.3 Table of Studies/Clinical Trials

Table 2 summarizes the clinical trials relevant to this BLA submission.

Table 2. Studies in the BLA application

Study Code	Study Population	Study Design	Treatment Arm
BIOS-16-001	Paediatric subjects aged ≥ 28 days (≥ 1 month) to < 18 years, requiring non-emergent open, hepatic, abdominal, retroperitoneal, pelvic, or thoracic (non-cardiac) surgical procedures.	Phase 3, open-label, single arm study	EVARREST
400-12-004	Paediatric subjects aged ≥ 28 days (≥ 1 month) to < 18 years, requiring non-emergent open, hepatic, abdominal, retroperitoneal, pelvic, or thoracic (non-cardiac) surgical procedures.	Phase 3, open-label, randomized study	EVARREST or SURGICEL was assigned randomly to each subject on a 1:1 basis

(Source: FDA reviewer's summary)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study BIOS-16-001

6.1.1 Objectives

To evaluate the safety and hemostatic effectiveness of EVARREST as an adjunct to controlling mild to moderate soft hepatic parenchyma or soft tissue bleeding during open

hepatic, abdominal, pelvic, retroperitoneal, and thoracic (non-cardiac) surgery in pediatric population.

6.1.2 Design Overview

This is an open label, prospective, multicenter, single arm clinical study evaluating EVARREST as an adjunct to hemostasis when conventional methods (i.e. suture, ligature, cautery) of controlling mild or moderate bleeding are ineffective or impractical during surgery in pediatric patients.

6.1.3 Population

Pediatric subjects, aged ≥ 28 days (≥ 1 month) to < 17 years, requiring non-emergent, open, hepatic, abdominal, retroperitoneal, pelvic, or thoracic (non-cardiac) surgical procedures.

Reviewer's Note: The Sponsor prespecified the pediatric population as subjects aged ≥ 28 days (≥ 1 month) to < 18 years. However, during the review of BLA 125392/645, the clinical team determined that the age range should be revised to ≥ 28 days (≥ 1 month) to < 17 years to align with the current standard. This revision does not affect the study results, as no subjects aged 17 to < 18 years were enrolled in this trial.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Once the target bleeding site (TBS) is identified during surgery, EVARREST is applied to fully cover the area with a slight overlap, followed by firm manual compression, often aided by a surgical sponge, for up to 4 minutes to control bleeding.

6.1.6 Sites and Centers

Subjects were enrolled and treated in 5 sites in the US and the UK.

6.1.7 Surveillance/Monitoring

Ongoing safety assessment was performed by the Sponsor (ETHICON, Inc.) throughout the study. The Sponsor monitor or designee contacted and visited Investigators regularly and was permitted to inspect trial records. Serious adverse events (SAEs) were required to be reported to (b) (4), the designated safety monitoring Contract Research Organization (CRO), within 24 hours of the Investigator becoming aware of the event. Suspected unexpected serious adverse reactions (SUSARs) were reported to relevant competent authorities, Principal Investigators, and IRBs/Ethics Committees within 7 calendar days (for fatal or life-threatening events) or 15 calendar days (for all other SUSARs).

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint:

- Absolute time to hemostasis (TTH), defined as the absolute time elapsed from TBS identification to the last moment in time at which detectable bleeding at the TBS was observed.

Secondary Endpoints:

- Proportion of subjects achieving hemostatic success at 4 minutes following TBS identification, with no TBS bleeding requiring treatment at any time prior to final fascial closure.
- Proportion of subjects achieving hemostatic success at 10 minutes following TBS identification, with no TBS bleeding requiring treatment at any time prior to final fascial closure.
- Proportion of subjects with no re-bleeding at the TBS.

Criteria for Study Success:

- Criteria for study success was not defined.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical considerations proposed in the study protocol and statistical analysis plan are described in the following:

Statistical Hypothesis:

Hypothesis testing was not performed or reported in this sBLA.

Multiplicity Adjustment:

None.

Analysis Populations:

All enrolled set (AES)

All subjects who provided an informed consent or assent form for this study.

Full analysis set (FAS or Intent to treat [ITT] set)

All enrolled and eligible subjects for whom TBS was identified. Subjects who did not complete the procedure after TBS identification were to be included in the FAS analysis.

Per protocol [PP] set

All FAS subjects who had no major protocol deviations affecting the primary effectiveness endpoint and had data available for this endpoint.

Safety analysis set

All subjects who received treatment.

Statistical Methods:

TTH was summarized using the point estimate and corresponding two-sided distribution-free 95% CI for descriptive purpose only.

All secondary endpoints were summarized descriptively using counts and percentages. In addition, two-sided 95% CIs were estimated for the proportion of success in EVARREST-treated subjects, using the Clopper-Pearson method.

Interim Analysis:

No interim analysis for efficacy was planned or performed.

Sample Size and Power Calculation:

No formal sample size calculation was performed for this study as no formal statistical hypotheses are being tested. However, a total of 35 subjects with an identified TBS were considered adequate by the Sponsor to provide sufficient information to evaluate data descriptively.

Missing Data and Imputation:

No missing data handling or imputation strategy was prespecified or performed for the primary analysis.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

Table 3. Key Demographic – All Enrolled Set

Characteristic	EVARREST N=35
Age at Consent (Years)	
N	35
Mean	4.59
SD	4.341
Median	3
Min, Max	0.7, 15.0
Pediatric Age Group, n (%)	
Infants and Toddlers (≥ 28 days to 23 months)	12 (34.3)
Children (2 to 11 years)	18 (51.4)
Adolescents (12 to <17 years)	5 (14.3)
Gender, n (%)	
Male	20 (57.1)
Female	15 (42.9)
Childbearing Potential (Female Subjects Only), n (%)	
N (females)	15
Yes	3 (20.0)
No	12 (80.0)
Race, n (%)	
White/Caucasian	20 (57.1)

Black/African American	9 (25.7)
Asian	3 (8.6)
American Indian or Alaska Native	0
Native Hawaiian/Other Pacific Islander	0
Other	3 (8.6)
Ethnicity, n (%)	
Hispanic	2 (5.7)
Non-Hispanic	33 (94.3)
Height (cm)	
N	33
Mean	104.2
SD	30.3
Median	100
Min, Max	69, 165
Weight (kg)	
N	35
Mean	22.3
SD	21.94
Median	14
Min, Max	7, 98
BMI (kg/m ²)	
N	33
Mean	17.89
SD	5.583
Median	16.5
Min, Max	12.3, 37.3

(Source: Adapted from BLA 125392/645.0 Module 5.3.5, FDA reviewer's summary)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 4. Summary of Surgical Information – All Enrolled Set

Characteristic	EVARREST N=35
Primary operative procedure, n subjects (%)	
Intra-abdominal	20 (57.1)
Intra-thoracic	0
Retroperitoneal	15 (42.9)
Pelvic	0
Other	0
Total surgical procedure time (first incision to last suture/staple), min	
Mean (SD)	185.6 (100.30)

Median (range)	166.0 (50, 498)
Time from surgery start (first incision) to initiation of final fascial closure, min	
Mean (SD)	152.9 (91.09)
Median (range)	136.0 (36, 422)

(Source: Adapted from BLA 125392/645.0 Module 5.3.5, FDA reviewer's summary)

Table 5. Summary of TBS Identification – All Enrolled Set

Characteristic	EVARREST N=35
Primary method used to obtain hemostasis, n (%)	
None (Other methods are impractical or inappropriate)	4 (11.4)
Suture	8 (22.9)
Ligation	1 (2.9)
Cautery	17 (48.6)
Other	5 (14.3)
TBS area (cm ²)	
Mean (SD)	13.541 (17.8249)
Median (range)	7.500 (0.04, 81.00)
Type of bleeding, n (%)	
Mild	20 (57.1)
Moderate	15 (42.9)
Location of TBS, n (%)	
Hepatic	20 (57.1)
Abdominal	6 (17.1)
Pelvic	0
Retroperitoneal	9 (25.7)
Thoracic (non-cardiac)	0

(Source: Adapted from BLA 125392/645.0 Module 5.3.5, FDA reviewer's summary)

6.1.10.1.3 Subject Disposition

Table 6. Subjects Disposition – All Enrolled Set

Characteristic	EVARREST N=35
All Enrolled Set (Signed Informed Consent or Assent Form)	35
Full Analysis Set ^a	31
Per-Protocol (PP) Analysis Set ^b	25
Safety Analysis Set	35
Completed the Study	35 (100.0%)

^a Excludes 4 subjects who had an ineligible TBS and therefore had an MPD affecting the inclusion criteria.

^b Excludes 10 subjects with an MPD affecting the primary endpoint.

(Source: Adapted from BLA 125392/645.0 Module 5.3.5, FDA reviewer's summary)

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary effectiveness endpoint was TTH, defined as the absolute time elapsed from TBS identification to the last moment at which detectable bleeding at the TBS was observed.

The Sponsor pre-specified the FAS (N=31) as the primary analysis population in the CSR. In the FAS, the median (range) TTH was 4.00 (4.0, 55.5) minutes, with a 95% DF CI for the median of (4.0, 4.0) and a mean (SD) of 7.62 (11.846) minutes.

During the review of sBLA 125392/645, however, the clinical team determined that the AES (N=35) would serve as the primary analysis population for labeling purposes. The AES includes 4 subjects with major protocol deviations affecting inclusion criteria (ineligible TBS on kidney parenchyma), who were excluded from the FAS. Despite this difference in population, the primary efficacy results were consistent between the two analysis sets. In the AES, the median (range) TTH was 4.00 (4.0, 55.5) minutes, with a 95% DF CI for the median of (4.0, 4.0) and a mean (SD) of 7.77 (11.150) minutes.

A supportive analysis conducted in the PP set (N=25) yielded results consistent with both the FAS and AES analyses, further supporting the robustness of the primary efficacy findings. In the PP set, the median (range) TTH was 4.00 (4.0, 55.5) minutes, with a 95% DF CI for the median of (4.00, 4.00) and a mean (SD) of 8.05 (13.142) minutes.

6.1.11.2 Analyses of Secondary Endpoints

Efficacy was further supported by the secondary effectiveness endpoints, including the proportion of subjects achieving hemostatic success at 4 minutes and 10 minutes following TBS identification, as well as the proportion of subjects with no re-bleeding at the TBS. Detailed results are summarized in Table 7.

Table 7. Secondary Effectiveness Endpoints – Full Analysis Set and All Enrolled Set

Variable	Category/Statistic	EVARREST FAS N=31	EVARREST AES N=35
Hemostatic success at 4 minutes, n (%)	Success	24 (77.4)	24 (68.6)
	95% CI for success	(58.90, 90.41)	(50.71, 83.15)
Hemostatic success at 10 minutes, n (%)	Success	29 (93.5)	33 (94.3)
	95% CI for success	(78.58, 99.21)	(80.84, 99.30)
Re-bleeding at the TBS, n (%) ^a	Re-bleeding	1 (3.2)	1 (2.9)

^a Bleeding at the TBS that is assessed as re-bleeding (or as both continuous bleeding and re-bleeding) CI, Confidence interval estimated using Clopper-Pearson methodology.

(Source: Adapted from BLA 125392/645.0 Module 5.3.5, FDA reviewer's summary)

6.1.11.3 Subpopulation Analyses

Table 8 presents the TTH results in the Full Analysis Set and All Enrolled Set by key baseline characteristics. The TTH remains relatively consistent across all evaluated subgroups.

Table 8. Subgroup Analysis by Key Demographic – Full Analysis Set and All Enrolled Set

Parameter	EVARREST FAS N=31	EVARREST AES N=35
Absolute Time to Hemostasis – Overall Group (minutes)		
Mean (SD)	7.62 (11.846)	7.77 (11.150)
Median (range)	4.00 (4.0, 55.5)	4.00 (4.0, 55.5)
95% DF CI for median	(4.00, 4.00)	(4.00, 4.00)
Subgroup by Bleeding Intensity ^a		
Mild Bleeding		
Number of subjects	20	20
Mean (SD)	4.01 (0.037)	4.01 (0.037)
Median (range)	4.00 (4.0, 4.2)	4.00 (4.0, 4.2)
Moderate Bleeding		
Number of subjects	11	15
Mean (SD)	14.20 (18.637)	12.78 (15.962)
Median (range)	4.75 (4.0, 55.5)	9.00 (4.0, 55.5)
Subgroup by Pediatric Group ^a		
Age ≥28 days to <1 year		
Number of subjects	4	4
Mean (SD)	14.80 (21.608)	14.80 (21.608)
Median (range)	4.00 (4.0, 47.2)	4.00 (4.0, 47.2)
Age ≥1 year to <17 years		
Number of subjects	27	31
Mean (SD)	6.56 (9.947)	6.86 (9.314)
Median (range)	4.00 (4.0, 55.5)	4.00 (4.0, 55.5)
Subgroup by Age Group ^a		
Infants and Toddlers (≥28 days to 23 months)		
Number of subjects	12	12
Mean (SD)	11.90 (18.526)	11.90 (18.526)
Median (range)	4.00 (4.0, 55.5)	4.00 (4.0, 55.5)
Children (2 to 11 years)		
Number of subjects	14	18
Mean (SD)	4.90 (2.101)	5.79 (2.635)
Median (range)	4.00 (4.0, 10.0)	4.00 (4.0, 10.0)

Adolescents (12 to <17 years)		
Number of subjects	5	5
Mean (SD)	5.00 (2.236)	5.00 (2.236)
Median (range)	4.00 (4.0, 9.0)	4.00 (4.0, 9.0)

^a Summary statistics are based on the number of subjects with non-missing data in the corresponding subgroup.

(Source: Adapted from BLA 125392/645.0 Module 5.3.5, FDA reviewer's summary)

6.1.11.4 Dropouts and/or Discontinuations

Refer to Table 6 Subjects Disposition in Section 6.1.10.1.3.

6.1.12 Safety Analyses

6.1.12.1 Methods

Descriptive statistics were used to summarize safety outcomes in the Safety Analysis Set.

6.1.12.3 Deaths

No deaths were reported during study BIOS-16-001.

6.1.12.4 Nonfatal Serious Adverse Events

Table 9 summarizes serious adverse events (SAE) by system organ class and preferred term, with a total of 13 individual SAEs reported in the Safety Analysis Set. Infections and Infestations was the only System Organ Class in which the number of events exceeded the number of subjects, with 3 events reported across 2/35 (5.7%) subjects.

Table 9. Summary of Serious Adverse Events by System Organ Class and Preferred Term
– Safety Analysis Set

System Organ Class / Preferred Term	EVARREST N=35	Events
Blood and lymphatic system disorders	3 (8.6%)	3
Febrile neutropenia	3 (8.6%)	3
Thrombocytopenia	0	0
Gastrointestinal disorders	0	0
Intussusception	0	0
Localised intraabdominal fluid collection	0	0
General disorders and administration site conditions	1 (2.9%)	1
Pyrexia	1 (2.9%)	1
Infections and infestations	2 (5.7%)	3
Catheter site infection	1 (2.9%)	1
Device related infection	0	0
Lower respiratory tract infection	1 (2.9%)	1
Respiratory syncytial virus infection	1 (2.9%)	1

Urinary tract infection	0	0
Injury, poisoning and procedural complications	3 (8.6%)	3
Post procedural bile leak	1 (2.9%)	1
Procedural pain	1 (2.9%)	1
Procedural vomiting	1 (2.9%)	1
Investigations	0	0
Weight decreased	0	0
Metabolism and nutrition disorders	1 (2.9%)	1
Dehydration	1 (2.9%)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0
Neuroblastoma	0	0
Nervous system disorders	1 (2.9%)	1
Syncope	1 (2.9%)	1
Renal and urinary disorders	0	0
Haematuria	0	0
Surgical and medical procedures	0	0
Central venous catheterisation	1 (2.9%)	1
Vascular disorders	0	0
Bloody discharge	0	0

(Source: Adapted from BLA 125392/645.0 Module 5.3.5, FDA reviewer's summary)

6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) include thromboembolic events (TEE) and rebleeding following application of the EVARREST patch. No TEEs were identified in the Safety Analysis Set. A total of 3 rebleeding events were reported across the Safety Analysis Set.

6.2 Study 400-12-004

6.2.1 Objectives

To evaluate the safety and hemostatic effectiveness of EVARREST as an adjunct to controlling mild to moderate soft hepatic parenchyma or soft tissue bleeding during open hepatic, abdominal, pelvic, retroperitoneal, and thoracic (non-cardiac) surgery in pediatric population.

6.2.2 Design Overview

This is an open label, prospective, randomized, multicenter, active-controlled, clinical study evaluating the safety and efficacy of EVARREST as an adjunct to control mild-to-moderate bleeding in pediatric subjects requiring non-emergent hepatic, abdominal, retroperitoneal, pelvic, or thoracic (non-cardiac) surgical procedures.

6.2.3 Population

Pediatric subjects, aged ≥ 28 days to < 17 years, requiring non-emergent, open, hepatic, abdominal, retroperitoneal, pelvic, or thoracic (non-cardiac) surgical procedures.

Reviewer's Note: The Sponsor prespecified the pediatric population as subjects aged ≥ 28 days (≥ 1 month) to < 18 years. However, during the review of BLA 125392/645, the clinical team determined that the age range should be revised to ≥ 28 days (≥ 1 month) to < 17 years to align with the current standard. This revision does not affect the study results, as no subjects aged 17 to < 18 years were enrolled in this trial.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Once the target bleeding site (TBS) is identified during surgery, EVARREST is applied to fully cover the area with a slight overlap, followed by firm manual compression, often aided by a surgical sponge, for up to 4 minutes to control bleeding.

6.2.6 Sites and Centers

Subjects were enrolled and treated in 5 sites in the UK. Although 3 sites in Belgium were initiated, no subjects were enrolled.

6.2.7 Surveillance/Monitoring

ETHICON designees were responsible for study activities such as site management, project management, data management, statistical analysis, clinical study report writing, and quality assurance. Other study activities, such as safety monitoring/reporting, were undertaken by (b) (4) and Ethicon. Study product management was undertaken by (b) (4). ETHICON performed site monitoring.

6.2.8 Endpoints and Criteria for Study Success

Primary Endpoint:

- Absolute time to hemostasis (TTH), defined as the absolute time elapsed from randomization to the last moment in time at which detectable bleeding at the TBS was observed.

Secondary Endpoints:

- Proportion of subjects achieving hemostatic success at 4 minutes following randomization and no bleeding requiring treatment at the TBS occurs any time prior to final fascial closure.
- Proportion of subjects achieving hemostatic success at 10 minutes following randomization and no bleeding requiring treatment at the TBS occurs any time prior to final fascial closure.
- Proportion of subjects with no re-bleeding at the TBS.

Criteria for Study Success:

- Criteria for study success was not defined.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Statistical considerations proposed in the study protocol and statistical analysis plan are described in the following:

Statistical Hypothesis:

Hypothesis testing was not performed or reported in this sBLA.

Multiplicity Adjustment:

None.

Analysis Populations:

All enrolled set (AES)

All subjects provided an informed consent or assent form for this study.

Full analysis set (FAS or Intent to treat [ITT] set)

All randomized subjects. Subjects who did not complete the procedure with the use of EVARREST or SURGICEL after randomization were to be included in the FAS analysis.

Per protocol [PP] set

All FAS subjects had no major protocol deviations affecting the primary effectiveness endpoint and had data available for this endpoint.

Safety analysis set

All subjects who received treatment.

Statistical Methods:

Descriptive statistical analyses were conducted by treatment group for the primary and secondary effectiveness endpoints. The primary effectiveness endpoint was also descriptively summarized by treatment group and pediatric group, as well as treatment group and age group. In addition, 95% distribution-free confidence intervals (CIs) for median absolute TTH were reported separately for EVARREST and Control groups.

Two-sided 95% CIs for the proportion of subjects with hemostasis at 4 minutes and 10 minutes were constructed for each treatment group separately, using the Clopper-Pearson method.

Interim Analysis:

No interim analysis for efficacy was planned or performed.

Sample Size and Power Calculation:

No formal sample size calculation was performed for this study as no formal statistical hypotheses are being tested. However, the sample size of at least 40 randomized subjects is considered adequate by the Sponsor to provide sufficient information to evaluate data

descriptively.

Missing Data and Imputation:

No missing data handling or imputation strategy was prespecified or performed for the primary analysis.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

6.2.10.1.1 Demographics

Table 10. Key Demographic – All Enrolled Set

Characteristic	EVARREST N=20	SURGICEL N=20
Age at Consent (Years)		
N	20	20
Mean (SD)	4.60 (4.193)	5.46 (4.778)
Median	3.00	4.00
Min, Max	0.8, 13.0	0.3, 14.0
Pediatric Age Group, n (%)		
Infants and Toddlers (≥28 days to 23 months)	6 (30.0%)	5 (25.0)
Children (2 to 11 years)	11 (55.0%)	11 (55.0)
Adolescents (12 to <17 years)	3 (15.0%)	4 (20.0)
Gender, n (%)		
Male	11 (55.0%)	13 (65.0)
Female	9 (45.0%)	7 (35.0)
Childbearing Potential (Female Subjects Only), n (%)		
N (females)	9	7
Yes	2 (22.2%)	1 (14.3)
No	7 (77.8%)	6 (85.7)
Race, n (%)		
White or Caucasian	18 (90.0%)	17 (85.0)
Black or African American	1 (5.0%)	0
Asian	0	1 (5.0)
American Indian or Alaska Native	0	0
Native Hawaiian/Other Pacific Islander	0	0
Other	1 (5.0%)	2 (10.0)
Ethnicity, n (%)		

Hispanic	1 (5.0%)	2 (10.0)
Non-Hispanic	19 (95.0%)	18 (90.0)
Height (cm)		
N	15	18
Mean (SD)	103.2 (28.63)	110.6 (35.04)
Median	97.0	104.0
Min, Max	67, 157	63, 174
Weight (kg)		
N	20	20
Mean (SD)	20.4 (14.87)	23.9 (19.87)
Median	14.5	18.0
Min, Max	6, 53	6, 79
BMI (kg/m ²)		
N	15	18
Mean (SD)	17.11 (2.841)	17.48 (3.834)
Median	16.80	15.90
Min, Max	13.4, 23.1	14.4, 29.4

(Source: Adapted from BLA 125392/645.0 Module 5.3.5, FDA reviewer's summary)

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 11. Summary of Surgical Information – All Enrolled Set

Characteristic	EVARREST N=20	SURGICEL N=20
Primary Operative Procedure, n subjects (%)		
Intra-Abdominal	12 (60.0%)	16 (80.0%)
Intra-Thoracic	1 (5.0%)	1 (5.0%)
Retroperitoneal	4 (20.0%)	1 (5.0%)
Pelvic	2 (10.0%)	1 (5.0%)
Other	1 (5.0%)	1 (5.0%)
Overall Surgical Procedure Time, mins		
Mean (SD)	215.1 (105.07)	217.9 (110.08)
Median	189.0	205.5
Min, Max	88, 476	55, 471
Time from Surgery Start to Initiation of Final Fascial Closure, mins		
Mean (SD)	178.0 (92.92)	178.5 (98.01)
Median	147.0	181.0
Min, Max	54, 396	34, 401

(Source: Adapted from BLA 125392/645.0 Module 5.3.5, FDA reviewer's summary)

Table 12. TBS Identification – All Enrolled Set

Characteristic	EVARREST N=20	SURGICEL N=20
Primary method used to obtain hemostasis, n (%)		
None (Other methods are impractical or inappropriate)	2 (10.0)	5 (25.0)
Suture	4 (20.0)	7 (35.0)
Ligation	1 (5.0)	0
Cautery	12 (60.0)	7 (35.0)
Other	1 (5.0)	1 (5.0)
TBS Area (cm ²)		
Mean (SD)	5.627 (5.6095)	14.842 (25.3061)
Median	4.000	4.000
Min, Max	0.04, 24.00	0.09, 105.00
Type of Bleeding, n (%)		
Mild	14 (70.0)	11 (55.0)
Moderate	6 (30.0)	9 (45.0)
TBS Location, n (%)		
Hepatic	8 (40.0)	11 (55.0)
Abdominal	2 (10.0)	3 (15.0)
Pelvic	3 (15.0)	1 (5.0)
Retroperitoneal	6 (30.0)	3 (15.0)
Thoracic (Non-Cardiac)	1 (5.0)	2 (10.0)

(Source: Adapted from BLA 125392/645.0 Module 5.3.5, FDA reviewer's summary)

6.2.10.1.3 Subject Disposition

Table 13. Subjects Disposition – All Enrolled Set

Characteristic	EVARREST N=20	SURGICEL N=20
All Enrolled Set	20	20
Full Analysis Set	20	20
Per-Protocol (PP) Set ^a	14	19
Safety Analysis Set	20	20
Completed the Study ^b	19	19

^a Excludes subjects with an MPD affecting the primary endpoint.

^b Excludes subjects with lost to follow up.

(Source: Adapted from BLA 125392/645.0 Module 5.3.5, FDA reviewer's summary)

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The primary effectiveness endpoint was TTH, defined as the absolute time elapsed from randomization to the last moment in time at which detectable bleeding at the TBS was observed.

The sponsor pre-specified the FAS as the primary analysis population in the CSR. During the review of sBLA 125392/645, the clinical team determined that the AES would serve as the primary analysis population for labeling purposes. However, because the AES and FAS include the same subjects in study 400-12-004, the results were unaffected by this change. In the AES analysis, the median TTH was 4.0 minutes in both groups. The EVARREST group had a mean (SD) of 9.88 (25.226) minutes and a range of (4.0, 117.0) minutes, with a 95% distribution-free CI of the median of (4.0, 4.0) minutes. The SURGICEL group had a mean (SD) of 7.75 (8.197) minutes and a range of (4.0, 39.0) minutes, with a 95% distribution-free CI of the median of (4.0, 7.62) minutes.

A supportive analysis conducted in the PP set yielded results consistent with the AES analyses, further supporting the robustness of the primary efficacy findings. In the PP analysis, the median TTH was 4.0 minutes in both groups. The EVARREST group had a mean (SD) of 4.08 (0.197) minutes and a range of (4.0, 4.6) minutes, with a 95% distribution-free CI of the median of (4.0, 4.0) minutes. The SURGICEL group had a mean (SD) of 6.11 (3.718) minutes and a range of (4.0, 18.5) minutes, with a 95% distribution-free CI of the median of (4.0, 7.62) minutes.

6.2.11.2 Analyses of Secondary Endpoints

Efficacy was further supported by the secondary effectiveness endpoints, including the proportion of subjects achieving hemostatic success at 4 minutes and 10 minutes following randomization, as well as the proportion of subjects with no re-bleeding at the TBS. Detailed results are summarized in Table 14.

Table 14. Secondary Effectiveness Endpoints – All Enrolled Set

Variable	Category/Statistic	EVARREST N=20	SURGICEL N=20
Hemostatic success at 4 minutes, n (%)	Success	16 (80.0)	12 (60.0)
	95% CI for success	(56.34, 94.27)	(36.05, 80.88)
Hemostatic success at 10 minutes, n (%)	Success	20 (95.0)	18 (90.0)
	95% CI for success	(75.13, 99.87)	(68.30, 98.77)
Re-bleeding at the TBS, n (%) ^a	Re-bleeding	1 (5.0)	2 (10.0)

^a Bleeding at the TBS that is assessed as re-bleeding (or as both continuous bleeding and re-bleeding) CI, Confidence interval estimated using Clopper-Pearson methodology. (Source: Adapted from BLA 125392/645.0 Module 5.3.5, FDA reviewer's summary)

6.2.11.3 Subpopulation Analyses

Table 15 presents the TTH results in the All Enrolled Set by key baseline characteristics. The TTH remains relatively consistent across all evaluated subgroups.

Table 15. Subgroup Analysis by Key Demographic – All Enrolled Set

Parameter	EVARREST N=20	SURGICEL N=20
Absolute Time to Hemostasis – Overall (minutes)		
Mean (SD)	9.88 (25.226)	7.75 (8.197)
Median (range)	4.00 (4.0, 117.0)	4.00 (4.0, 39.0)
95% DF CI for median	(4.00, 4.00)	(4.00, 7.62)
Subgroup by Bleeding Intensity ^a		
Mild Bleeding		
Number of subjects	14	11
Mean (SD)	4.29 (0.935)	7.73 (10.527)
Median (range)	4.00 (4.0, 7.5)	4.00 (4.0, 39.0)
Moderate Bleeding		
Number of subjects	6	9
Mean (SD)	22.93 (46.085)	7.78 (4.590)
Median (range)	4.00 (4.0, 117.0)	6.90 (4.0, 18.5)
Subgroup by Pediatric Group ^a		
Age ≥28 days to <1 year		
Number of subjects	1	3
Mean (SD)	4.00 (-)	5.63 (1.484)
Median (range)	4.00 (4.0, 4.0)	6.00 (4.0, 6.9)
Age ≥1 year to <17 years		
Number of subjects	19	17
Mean (SD)	10.19 (25.878)	8.13 (8.862)
Median (range)	4.00 (4.0, 117.0)	4.00 (4.0, 39.0)
Subgroup by Age Group ^a		
Infants and Toddlers (≥28 days to 23 months)		
Number of subjects	6	5
Mean (SD)	4.00 (0.000)	4.98 (1.379)
Median (range)	4.00 (4.0, 4.0)	4.00 (4.0, 6.9)
Children (2 to 11 years)		
Number of subjects	11	11
Mean (SD)	14.37 (34.039)	9.83 (10.658)
Median (range)	4.00 (4.0, 117.0)	4.00 (4.0, 39.0)
Adolescents (12 to <17 years)		
Number of subjects	3	4
Mean (SD)	5.17 (2.021)	5.50 (3.000)
Median (range)	4.00 (4.0, 7.5)	4.00 (4.0, 10.0)

^a Summary statistics are based on the number of subjects with non-missing data in the corresponding subgroup.
(Source: Adapted from BLA 125392/645.0 Module 5.3.5, FDA reviewer's summary)

6.2.11.4 Dropouts and/or Discontinuations

Refer to Table 13 Subjects Disposition in Section 6.2.10.1.3.

6.2.12 Safety Analyses

6.2.12.1 Methods

Descriptive statistics were used to summarize safety outcomes in the Safety Analysis Set.

6.2.12.3 Deaths

No deaths were reported during study 400-12-004.

6.2.12.4 Nonfatal Serious Adverse Events

Table 16 summarizes serious adverse events (SAE) by system organ class and preferred term. In the EVARREST group, a total of 7 events were reported across 6 system organ classes. The most frequently affected system organ classes were Blood and lymphatic system disorders, Gastrointestinal disorders, Infections and infestations, Investigations, and Renal and urinary disorders, each occurring in 1/20 (5.0%) subjects.

In the SURGICEL group, a total of 8 events were reported across 5 system organ classes. Blood and lymphatic system disorders was the only SOC with more than one event, with 2 events reported in 1/20 (5.0%) subjects. Neoplasms (neuroblastoma) and Vascular disorders (bloody discharge) were each reported in 1/20 (5.0%) subjects in the SURGICEL group only

Table 16. Summary of Serious Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set

System Organ Class / Preferred Term	EVARREST N=20		SURGICEL N=20	
	Subjects	Events	Subjects	Events
Blood and lymphatic system disorders	1 (5.0%)	1	1 (5.0%)	2
Febrile neutropenia	1 (5.0%)	1	1 (5.0%)	1
Thrombocytopenia	0	0	1 (5.0%)	1
Gastrointestinal disorders	1 (5.0%)	1	1 (5.0%)	1
Intussusception	1 (5.0%)	1	0	0
Localised intraabdominal fluid collection	0	0	1 (5.0%)	1
General disorders and administration site conditions	0	0	0	0
Pyrexia	0	0	0	0
Infections and infestations	1 (5.0%)	1	1 (5.0%)	1

Catheter site infection	0	0	0	0
Device related infection	0	0	1 (5.0%)	1
Lower respiratory tract infection	0	0	0	0
Respiratory syncytial virus infection	0	0	0	0
Urinary tract infection	1 (5.0%)	1	0	0
Injury, poisoning and procedural complications	0	0	0	0
Post procedural bile leak	0	0	0	0
Procedural pain	0	0	0	0
Procedural vomiting	0	0	0	0
Investigations	1 (5.0%)	1	0	0
Weight decreased	1 (5.0%)	1	0	0
Metabolism and nutrition disorders	0	0	0	0
Dehydration	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (5.0%)	1
Neuroblastoma	0	0	1 (5.0%)	1
Nervous system disorders	0	0	0	0
Syncope	0	0	0	0
Renal and urinary disorders	1 (5.0%)	1	0	0
Haematuria	1 (5.0%)	1	0	0
Surgical and medical procedures	0	0	0	0
Central venous catheterisation	0	0	0	0
Vascular disorders	0	0	1 (5.0%)	1
Bloody discharge	0	0	1 (5.0%)	1

(Source: Adapted from BLA 125392/645.0 Module 5.3.5, FDA reviewer's summary)

6.2.12.5 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) include thromboembolic events (TEE) and rebleeding following application of the EVARREST patch. No TEEs were identified in the Safety Analysis Set. There were 5 rebleeding events reported in the 400-12-004 study, with 4 events in the SURGICEL group, and 1 in the EVARREST group.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

sBLA 125392/645 presented efficacy data from two pediatric studies, an open-label, prospective, non-controlled, multicenter study conducted in the US and UK (BIOS-16-001; N=35) and a randomized, controlled study in the UK (400-12-004; N=40), to fulfill the PREA PMR and expand the indication to adjunctive hemostasis in both adult and pediatric populations.

TTH was the primary efficacy endpoint in both studies, though defined differently. In BIOS-16-001, TTH was measured from TBS identification to the last observed moment of detectable bleeding, whereas in 400-12-004, TTH was measured from randomization to the last observed moment of detectable bleeding at the TBS. Across both studies, EVARREST achieved a median TTH of 4.0 minutes in the AES. In BIOS-16-001, the mean (SD) TTH was 7.77 (11.150) minutes. In 400-12-004, the mean (SD) TTH was 9.88 (25.226) minutes in the EVARREST group and 7.75 (8.197) minutes in the SURGICEL group.

No deaths were reported in either study. SAEs were reported in 13 subjects in BIOS-16-001, and in 7 and 8 subjects in the EVARREST and SURGICEL groups, respectively, in 400-12-004. No TEEs were identified. Rebleeding events totaled 3 in BIOS-16-001, and 1 (EVARREST) and 4 (SURGICEL) in 400-12-004.

10.2 Conclusions and Recommendations

I have reviewed and verified the efficacy analyses for Studies BIOS-16-001 and 400-12-004. The efficacy results were consistent across both studies, providing sufficient evidence supporting the approval of Fibrin Pad as an adjunct to hemostasis across a broad range of surgical scenarios in both adult and pediatric subjects in this sBLA.

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